REMARKS

Claims 2, 14-15, and 19-21 are pending after entry of this paper. Claims 1-19 have been rejected. Claims 1, 3-13, and 16-18 have been cancelled without prejudice. Amendments and cancellations have been made solely for the purpose of furthering prosecution, and in no way constitute prejudice towards or waiver of any subject matter therein. Applicants expressly reserve the right to pursue cancelled claims in a continuing application.

Claims 2, 14-15, and 19 have been amended, and claims 20-21 have been newly added. Support may be found throughout the instant specification. No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Rejections under 35 U.S.C. §112

The Examiner has rejected claims 1-19 under 35 U.S.C. §112, first paragraph for allegedly failing to satisfy the enablement requirement. Specifically, the Examiner contends that the specification is not enabling for the entrapping of "other substance." In accordance with the Examiner's suggestion, and solely for the purpose of furthering prosecution, applicants have cancelled the term "other substance" from the claims. Accordingly, applicants respectfully request withdrawal of this rejection.

The Examiner has rejected claims 1-13 under 35 U.S.C. §112,, second paragraph for allegedly being indefinite. Regarding claims 1, 2, 11, and the claims which depend therefrom, the Examiner contends that the phrase "or other substance" renders the claims indefinite. As above, and solely for the purpose of furthering prosecution, applicants have

cancelled the term "or other substance" from the claims. Accordingly, applicants respectfully request withdrawal of this rejection.

In light of the cancellation of claim 6, applicants submit that the rejection to claim 6 under 35 U.S.C. §112, second paragraph is now moot.

Applicants thus believe that all claims are in full compliance with the requirements of 35 U.S.C. §112, and respectfully request reconsideration and withdrawal of the rejections.

Response to Rejections under 35 U.S.C. §102

The Examiner has rejected claims 1, 2, and 5 under 35 U.S.C. §102(b) as allegedly being anticipated by Henrichs et al (U.S. Patent No. 6,424,857), Baker (U.S. Patent No. 6,471,968), or Feldheim et al (U.S. Patent No. 6,602,932). Amended claim 2 remains pending, and is addressed below.

Regarding Henrichs et al, the Examiner specifically contends that Henrichs et al teaches polymeric nanoparticles attached to a fluorescent dye (citing to col. 8, lines 8-18) , which the Examiner alleges meets the claim limitations. Applicants respectfully disagree.

Henrichs et al is broadly directed to physiologically tolerable contrast agents. The contrast agents of Henrichs et al are specifically acousto-optical and/or sonoluminescent (see abstract and col. 2 lines, 32-67). Henrichs et al does not describe attaching dyes to liposomes; rather, Henrichs et al describes liposomes with dyes enclosed (col. 8, lines 3-4).

The Examiner contends that the nanoliposomes of Henrichs et al are indeed polymeric nanoparticles, as required by claim 2, or biodegradable polymeric nanoparticles, as required by claim 3. Applicants respectfully assert that liposomes, as described by Henrichs et al, are not polymeric nanoparticles, but instead are vesicles (see col. 8, lines 3-7, applicants note the typo in the referenced WIPO publication, which should be WO 96/23524). More specifically, liposomes are spherical vesicles composed of a bilayer membrane of an amphiphilic material, such as a phospholipids or cholesterol. Furthermore, the liposomes as described by Henrichs et al, as vesicles, contain central voids in which the dye is enclosed. This is in contrast to claim 2, which requires that the dye be "entrapped within the matrix" of a polymeric nanoparticle.

Regarding Baker, the Examiner specifically contends that Baker teaches nanosized polymeric dendrimers that can bind many substances, which the Examiner alleges meets the claim limitations. Applicants respectfully disagree.

Baker is directed to dendrimer based multifunctional compositions (abstract). The dendrimers of Baker can broadly include components for "targeting, imaging, sensing, and/or triggering release of a therapeutic or diagnostic material" (col. 2, lines 36-37). Applicants note that Baker discloses neither indocyanine green, nor any of the polymers as recited in amended claim 2. Thus, applicants respectfully request withdrawal of the rejection over Baker.

Regarding Feldheim et al, the Examiner specifically contends that Feldheim et al teaches polymeric nanoparticles with a shell on their surface, which allegedly means that the particles are capable of entrapping a substance. Applicants respectfully disagree.

Feldheim et al is directed to polymeric nanoparticle shells for guest encapsulation. Specifically, Feldheim et al discloses methods of synthesizing a nanocapsule by polymerizing a

monomer on a nanoparticle template (abstract). The nanocapsules are "hollow nanometer-sized capsules" (col. 1, lines 18-19) capable of carrying a guest molecule within the hollow void. In contrast, instant claim 2 requires that that the guest (e.g., fluorescent dye molecule) be "entrapped within the matrix" of a polymeric nanoparticle. Feldheim et al does not disclose a structure where the guest is within the polymeric matrix. Furthermore, Feldheim et al discloses neither indocyanine green nor any of the polymers recited in amended claim 2.

For the foregoing reasons, applicants respectfully request reconsideration and withdrawal of the rejections over Henrichs et al, Baker, and Feldheim.

The Examiner has rejected claims 1, 2, and 6 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 4,267,235 ("Rembaum et al"), U.S. Patent No. 5,073,498 ("Schwarz et al"), or U.S. Patent No. 5,395,688 ("Wang et al"). Amended claim 2 remains pending, and is addressed below.

The Examiner specifically contends that the references (abstract and claims) teach fluorescent microparticles comprising a fluorescent dye entrapped in a microparticle. Applicants respectfully disagree.

Rembaum et al is directed to polyglutaraldehyde microspheres. Rembaum et al teaches that fluorescent microspheres are prepared by addition of a fluorochrome during polymerization (abstract), whereby the microspheres have reacted with the fluorochrome (claims). In contrast, claim 2 requires the fluorescent dye to be "entrapped within the matrix" of a polymeric nanoparticle, as opposed to covalently bound. Furthermore, Rembaum et al discloses neither indocyanine green nor any of the polymers recited in amended claim 2.

Schwarz et al is directed to fluorescent microbeads for use in alignment of a flow cytometer or fluorescent microscope (abstract). The microbeads of Schwarz et al are prepared by a process requiring polymerization of the microbeads in the presence of a fluorescent dye (col. 3, lines 28-36), resulting in microbeads wherein the dye is covalently bound to the polymer (see, e.g., claim 3 of Schwarz et al). In contrast claim 2, requires the fluorescent dye to be "entrapped within the matrix" of a polymeric nanoparticle, as opposed to covalently bound. Furthermore, Schwarz et al discloses neither indocyanine green nor any of the polymers recited in amended claim 2.

Wang et al is directed to magnetically responsive fluorescent polymer particles prepared by coating a core polymer particle with a layer of polymer containing magnetically responsive metal oxide (abstract). Wang et al discloses neither indocyanine green nor any of the polymers recited in amended claim 2.

For the foregoing reasons, applicants respectfully request reconsideration and withdrawal of the rejections over Rembaum et al, Schwartz et al, and Wang et al.

The Examiner has rejected claims 1-4 and 6-19 under 35 U.S.C. §102(a) or (e) as allegedly anticipated by U.S. Patent No. 6,964,747 ("Banarjee et al"). Applicants respectfully submit that Banarjee et al is not available as prior art against the instant application, and thus request withdrawal of the rejection.

Banarjee et al is a U.S. Patent that issued from U.S. Application Serial No. 10/348,123, filed on January 21, 2003. The instant application is a national stage entry under 35 U.S.C. §371 of International Application No. PCT/US04/01472 filed January 15, 2004, claiming priority to U.S. Provisional Application No. 60/440,658 filed January 16, 2003. Applicants

respectfully assert that pending claims 2-18 and 21 are all fully supported by the provisional application.

Regarding claim 19, applicants respectfully assert that Banarjee et al. neither discloses nor suggests the use of a polymeric microparticle for the treatment of cancer. Regarding claim 20, applicants respectfully assert that Banarjee et al. neither discloses nor suggests the cellular uptake properties of the polymer microparticle.

For the foregoing reasons, applicants respectfully request reconsideration and withdrawal of the rejections over Banarjee et al.

The Examiner has rejected claims 1-19 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 6,268,222 ("Chandler et al").

Chandler et al is directed to a "core or carrier particle having on it's surface a plurality of smaller polymeric particles or nanoparticles, which are stained with different fluorescent dyes" (abstract). Although Chandler et al cites cyanine dyes in general (col. 7, lines 62-63), Chandler et al describes that organic-soluble (i.e., hydrophobic) dyes are contemplated (col. 8, lines 7-8). Chandler et al goes on to recite a laundry list of "equally suitable dyes" with no common property or thread among them (col. 8, line 34 – col. 9, line 24). Regarding the polymer, Chandler et al teaches that polystyrene is preferred, and goes on to recite a laundry list of polymers with no common property or thread among them (col. 3, lines 22-43). Chandler et al discloses that the stained nanoparticles are prepared by covalent attachment of the dye to the nanoparticle, polymerization of the nanoparticle in the presence of the dye, or diffusively dyeing a pre-formed nanoparticle (col. 10, lines 21-42).

Regarding amended claim 2, in the first instance, Chandler et al does not disclose indocyanine green. Furthermore, Chandler et al teaches away from the use of indocyanine green, a hydrophilic dye, by suggesting that organic-soluble dyes are contemplated for use. Additionally, applicants respectfully submit that the methods disclosed by Chandler et al will not result in a composition where indocyanine green is "entrapped within the matrix of a spherical or nearly spherical nanoparticle," as required by claim 2, because of the hydrophilic/hydrophobic repulsive interactions that result from using indocyanine green with the polymers recited in claim 2. Using the disclosure of Chandler et al, one of ordinary skill in the art would not arrive at a composition as claimed in claim 2, but rather would arrive at a composition with the hydrophilic dye congregated on the surface of the hydrophobic polymeric nanoparticle. As such, applicants respectfully submit that Chandler et al neither anticipates nor renders obvious the composition recited in amended claim 2.

Regarding claims 15-17, the Examiner cites col. 4, line 30 to col. 5, line 5 of Chandler et al. Applicants respectfully assert that neither the cited portion of Chandler et al nor Chandler et al as a whole disclose the use of a such a nanoparticle complex as a contrast agent as required by claims 15. The cited portion of Chandler et al refers broadly to "methods of using such particles for various diagnostic, analytic, and industrial applications known in the art" (col. 4, lines 31-32), but fails to specifically disclose or even suggest use as a contrast agent. This deficiency is not remedied by the working examples, which fail to disclose or even suggest use of such a composition as a contrast agent. Applicants submit that claim 15 is thus further distinguished over Chandler et al.

Regarding cancelled claim 18 (related to new claim 21), the Examiner does not detail a relevant rejection.[1] Furthermore, applicants respectfully assert that Chandler et al does not disclose the use of polymeric nanoparticles to entrap a fluorescent dye as a method of stabilizing, nor does Chandler expressly demonstrate enhanced stabilization compared to dye alone (as in claim 21). Indeed, Chandler et al. teaches the preferable selection of a dye with "improved photostability" (col. 9, lines 37-40), whereas claim 21 is directed to the enhancement of stabilization of a dye by means of entrapment in a polymeric nanoparticle. Applicants submit that claim 21 is thus further distinguished over Chandler et al.

Regarding claim 19, the Examiner states "[f]or cancer treatment, see col. 24, lines 34-42, where manufacturing drugs using nanoparticles is suggested." In the first instance, assuming *arguendo* that the Examiner's statement is accurate, such a rejection is not a proper rejection under 35 U.S.C. §102, as each and every element of the claim is not expressly taught in a single reference. Furthermore, the Examiner is incorrect in stating that manufacturing drugs using nanoparticles is suggested. The cited portion of Chandler et al instead refers to assays, *i.e.*, analytical techniques. Chandler et al. discloses no pharmaceuticals or drugs whatsoever, let alone drugs manufactured with polymeric nanoparticles and fluorescent dye. Of particular note, Chandler et al does not disclose the treatment of cancer. Applicants submit that claim 19 is thus further distinguished over Chandler et al.

Regarding new claim 20, applicants respectfully submit that Chandler et al neither expressly discloses nor suggests the enhanced cellular uptake of encapsulated dye compared to dye alone. Indeed, Chandler et al is completely silent as to intracellular uptake properties. Applicants submit that claim 20 is thus further distinguished over Chandler et al.

[1] The Examiner refers to claims 18-19 as a unit, but only cites a portion of Chandler et al allegedly regarding cancer treatment (see page 6 of the Office Action).

For the foregoing reasons, applicants respectfully request reconsideration and withdrawal of the rejection of the claims over Chandler et al.

Response to Rejections under 35 U.S.C. §103(a)

The Examiner has rejected claim 14 under 35 U.S.C. §103(a) for allegedly being obvious over Chandler et al alone. The Examiner specifically contends that it would have been obvious to assemble a PLGA nanoparticle ICG dye complex because ICG is a known near-IR dye and because Chandler et al teach microspheres preferably comprising a near-IR dye. In the first instance, applicants respectfully submit that for at least similar reasons as to why independent claims 2 is believed allowable, as discussed in detail above, claim 14 is also allowable. Furthermore, applicants submit that it would not have been obvious to assemble a composition comprising ICG entrapped within the matrix of a PLGA nanoparticle as required by claim 14 given the disclosure of Chandler et al because of the particular properties of indocyanine green and PLGA. Specifically, it is well-known that indocyanine green is a hydrophilic dye, and that PLGA is a hydrophobic polymer. As such, one of ordinary skill in the art would not be able to use the teachings of Chandler et al to construct such a complex, because, as described above, one of ordinary skill in the art would not have predicted success, specifically because of the expected repulsive hydrophilic/hydrophobic interaction.

For the foregoing reasons, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) over Chandler et al.

Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claims 2 and 14 from which all of the dependent claims depend are believed allowable as discussed above, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4424-4000US1.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4424-4000US1.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

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By: /Andrew D. Cohen/
Andrew D. Cohen
Registration No. 61,508

Correspondence Address:
MORGAN & FINNEGAN, L.L.P.
3 World Financial Center
New York, NY 10281-2101
(212) 415-8700 Telephone
(212) 415-8701 Facsimile